An Approach to Detecting Delayed Effects of Radioactive Contamination on Industrial–Urban-Area Dwellers

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Detecting changes in humans that result from radioactive contamination of the area of residence many years after an incident (i.e., when the radiation has substantially decayed) presents a difficult epidemiological problem. Problems of this kind are even more complicated in areas where the population is continually exposed to other harmful man-made factors. The city of Kamensk-Uralsky (Sverdlovsk region, Russia) is a good case in point. In 1957, part of Kamensk-Uralsky was contaminated as the result of an accident at the Kyshtym nuclear plant. In addition, the population of the contaminated area is being exposed to atmospheric emissions from several industrial enterprises. Two comparable groups of residents were formed: one in the contaminated area and another in a control area within the same city characterized by similar levels of chemical pollution but substantially lower radioactive contamination. The groups were composed of only those people who had been living in these areas continually since time of the accident and who were under 15 years of age at the time of the accident. The groups were matched by sex, age, and socio-occupational characteristics. For each subject, data were gathered on more than 50 parameters including hematological, immunological, and biochemical indices of the health status. All these data were obtained from blood tests taken in the fall of 1992. Data processing was carried out with the the help of a computerized mathematical pattern recognition methodology, which ensured reliable discrimination between the generalized health status in the areas under study. We found that the health status of inhabitants of the area more contaminated with radioactive fallouts was adversely affected by radiation.
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Vast radioactive contamination as a result of nuclear tests, accidents at nuclear plants, or even normal operation of nuclear plants has become a global ecological problem, whose importance was so dramatically brought to light by the Chernobyl accident. Although such catastrophes could probably be avoided, no one can guarantee with certainty that industrial nuclear plants will operate without accidents or that they will ever be provided with 100% closed-circuit (absolutely wasteless) technology. Radioactive contamination of an area that presents a direct hazard to human health brings about the need to move its population to safety. Detection of radioactive contamination effects requires long-term monitoring of changes in the health status of these people.

At the same time, many more people live in areas with considerably lower levels of radioactive contamination, but which still exceed the background level, because it is practically impossible to move the people from the area. Meanwhile, the question to what extent living in such an area is dangerous has not been answered unambiguously. Any epidemiological approach to this problem is necessarily retrospective. However, the results of epidemiological studies could provide a basis for predicting the consequences (including delayed effects) of living within zones of "moderate" radioactive contamination. From this viewpoint, the health status of the population in areas that have been contaminated for decades are of special interest. One such area, located in the Southern and Middle Urals of Russia, was contaminated in 1957 as the result of a nuclear accident at Kyshtym.

Changes in human health under such conditions are certain to be nonspecific. In other words, similar changes in health may occur in populations that have not been exposed to additional radiation. Epidemiologically, the problem consists of detecting a higher incidence of a health effect and associating it with radiation exposure. The difficulties of this problem are aggravated in areas where the same changes might be caused by continuous exposure to other man-made factors (toxic, mutagenic, carcinogenic, etc.). In these circumstances, practically any effect detected may be attributed to a combination of exposures and should be regarded as a complex "ecological pathology." This situation is observed in the industrial–urban area under discussion, whose residents make up the dominant part of the exposed population. However, it is important to discriminate changes in health associated with radioactive contamination from the background of complex ecological pathology. The necessity of this discrimination is dictated by considerations of scientific analysis but also by local problems including legal responsibility of contaminating plants.

There are a variety of epidemiological approaches to this problem. Our approach is characterized by some unconventional features, and here we describe the method itself rather than the specific results of the study. We believe that this approach could be applied to other problems of this kind. Nevertheless, we think the background of the Kyshtym accident and the general ecological situation in the region under study should precede the methodological part.

Region under Study

The Kyshtym accident happened in September 1957 when malfunctions in the cooling system set off an explosion of the radioactive liquid wastes (predominantly in the form of nitrates and acetates of various radionuclides) due to self-heating (*1,2*). As a result, 2×10^7 Ci of radioactive substances were emitted into the atmosphere. A northeast wind carried the radioactive plume, which gradually precipitated on the territory of the Chelyabinsk, Sverdlovsk, and Tyumen regions and formed a contaminated strip in 11 hr. In terms of the double global ^{90}Sr level, the accident contaminated an area 300 km in length and 30–50 km in width. The area with an average level of ^{90}Sr contamination of 2 Ci/km^2 (which was 40 times as high as the global level) measured 105 km × 6–8 km.

After the initial contamination, however, ^{90}Sr in equilibrium with ^{90}Y accounted for only 5.4% of the total activity, to which a major contribution was made by short-lived β-γ radionuclides (specifically, ^{144}Ce + ^{144}Pr and ^{95}Zr + ^{95}Nb accounted for 90.9% of the activity). In 3 years the total level of radioactive contamination decreased (mainly as a result of radioactive decay and partly because of migration) by a factor of 10 on average, and in 25 years it decreased to 3% of the initial level. At the present time ^{90}Sr + ^{90}Y accounts for 99.3% of the total radioactivity. The remaining 0.7% is contributed by another long-lived radionuclide that occurred in the radioactive wastes, namely, ^{137}Cs. Reductions in the level of radioactivity were accompanied by changes in the type of exposure to radiation in the contaminated area. At the early stages, exposure of the entire body to external γ-radiation

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played a major part, along with exposure of the gastrointestinal tract to γ- and β-radiation from contaminated food. Later on, the main hazard was the accumlation of ^{90}Sr in the skeleton and exposure of the bone marrow to β-radiation.

During the first 7–10 days after the accident, 600 people were moved out of the contaminated area, followed by another 6480 people during the year. In the second year 3100 people were evacuated. The urgency of evacuation depended on the average contamination of territory (from 500 Ci $^{90}Sr/km^2$ in the first group to 3.3 Ci $^{90}Sr/km^2$ in the last group). None of the people in the area with an average ^{90}Sr contamination of about 1 Ci/km^2 were evacuated. This area included part of the territory of Kamensk-Uralsky (Sverdlovsk region), the largest city in the entire contaminated zone. The greater part of this city had contamination levels <1 Ci/km^2.

In 1967 the same nuclear plant once again became a source of atmospheric radioactive contamination. As a result of drought in the summer that year, the bottom of the lake that had been used for storing radioactive wastes was exposed, and the dried sediment was carried away by wind. In this case the spreading time was longer than after the 1957 accident. Changes in wind direction during this time resulted in less defined boundaries of contamination as compared with the initial area. The composition of radionuclides was also different, with a considerably lower contribution from short-lived β– and γ-radionuclides to the total activity. This new, superimposed radioactive contamination has made epidemiological studies within the area of the Kyshtym accident even more complicated. But whatever the level of the repeat radioactive exposure in this area, the radiation doses from the 1957 Kyshtym accident were more significant, at least for the population that lived there in 1957 or in subsequent years. The difference in exposure between the exposed residents of Kamensk-Uralsky and those who lived outside the zone of highest contamination are still great. Moreover, in 1967 the contamination gradient within the city area featured the same pattern as in 1957 because the pattern of dominating winds did not change greatly. This means that the same areas suffered greatest contamination once again.

Kamensk-Uralsky is an old, heavily industrialized city in the Middle Urals with an aluminum plant, foundry, nonferrous metal processing plant, large thermal power station, and other plants. The emissions of these industrial enterprises pollute the atmosphere with fluoride, polycyclic aromatic hydrocarbons, lead, copper, some other toxic metals, fly ash, and sulfuric anhydride. Traffic in the city is also heavy, adding the toxic components of exhaust to the pollution of the lower layers of the atmosphere. All this creates an unfavorable ecological background, which makes the problem of detecting the health effects of past radiation exposure an extremely difficult if not impracticable task.

Study Plan

Our goal was to answer two interrelated questions: First, is it possible to clearly reveal the health effects of living in the area contaminated by radioactive fallout on the health of the population in Kamensk-Uralsky against the unfavorable general ecological background? Second, if the answer to the first question is yes, which features can be used for preclinical diagnosis of harmful effects?

With these questions in mind, we tried to eliminate as much as possible the effects of nonradiation factors by comparing the health status of "control" groups that differed from exposed groups in regard to radiation exposure. Taking into account the pilot character of the study, we selected a group of residents from the contaminated area who likely suffered the greatest exposure to radiation and, at the same time, were more sensitive to it.

The methodological scheme based on these assumptions is shown in Figure 1. First, it was necessary to choose base areas in the city for selecting the groups. Such areas were located sufficiently close to each other to ensure that they were similar, if not identical, in regard to industrial (nonradioactive) contamination. The city plan, and the condition of the infrastructures,

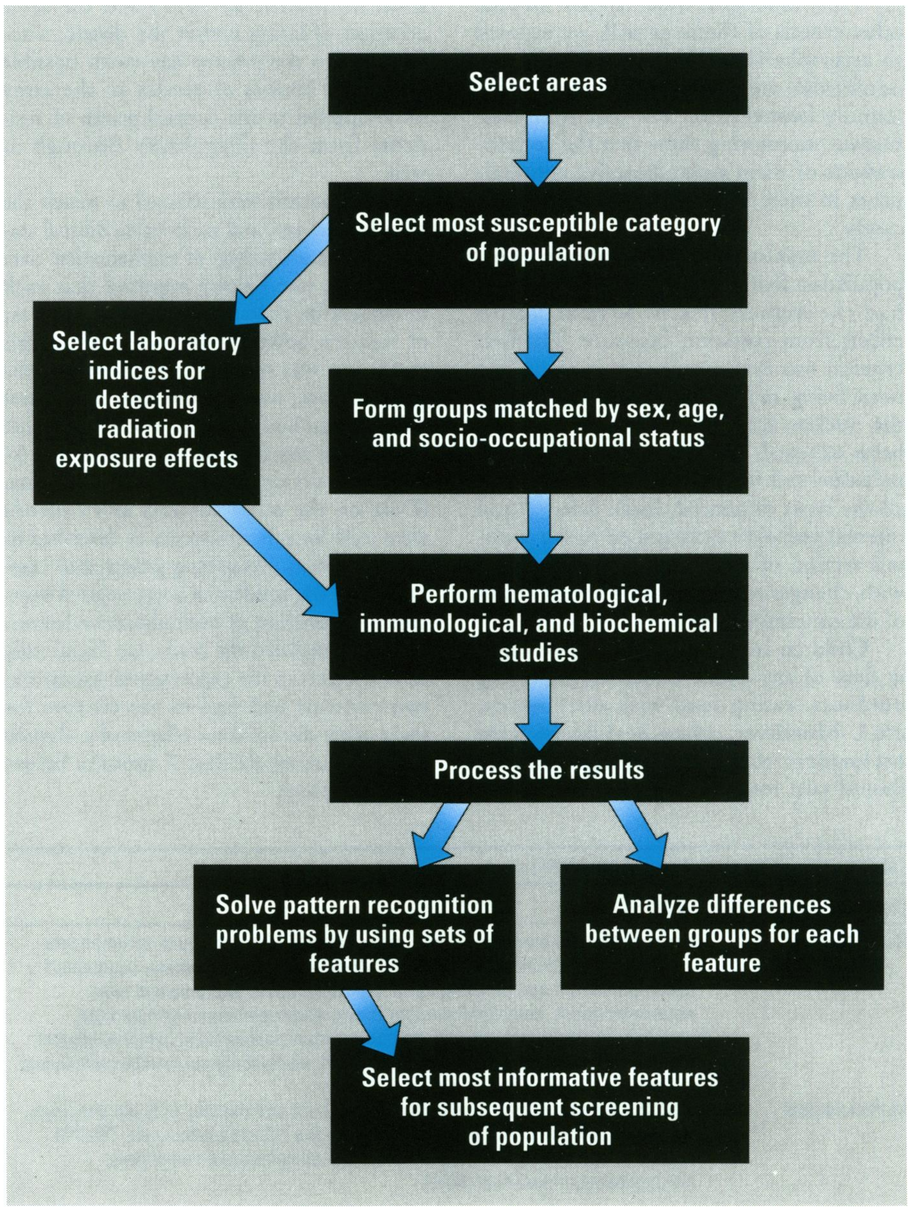

Figure 1. Flowchart for studying radiation exposure effects on the health status of the residents of Kamensk-Uralsky.

including health service, traffic, sanitation, etc., were also similar. At the same time, there was a sufficently marked difference between them in the level of radioactive contamination, at least during the initial period of high intensity. The fact that only part of Kamensk-Uralsky was significantly contaminated as a result of the accident made the task easier, since two zones of the same administrative division, i.e., the Leninsky Borough (together with some villages engulfed by the growing city) and the Oktyabrsky Borough, were located inside and outside the area of the highest contamination, respectively. The level of radioactive contamination in these areas differed by an order of magnitude, on average. In 1967 the Oktyabrsky Borough received at most half as much additional contamination as the Leninsky Borough.

These boroughs, which largely met the other criteria of choice as well, are exposed to atmospheric pollution, mainly from a nonferrous metal-processing plant and a foundry located there. The data from continuous monitoring show that the concentrations of main nonradioactive contaminants in these zones do not differ significantly.

The next step was to determine which population living in the Leninsky Borough had the highest risk of adverse health effects from radiation exposure. The first criteron was that people in this group had been living in this area since the time of the nuclear accident (i.e., those who had been exposed to the maximum dose of radiation and were subject to the effects of all the types of general, local, external and internal radiation as described in the previous section of this paper, which changed with changes in the isotopic composition of the contamination).

Children are always likely to get a higher dose of any contaminant (from playing outdoors, eating food with dirty hands, etc.). Moreover, when dealing with an osteotropic element like strontium, we should take into account that its incorporation in the bone tissue is more effective during the period of intensive growth and calcification of the skeleton. Finally, the processes of cell proliferation in all tissues are more intensive in children than in adults, which makes children more susceptible to radioactivity. These three considerations explain why the relative risk of death of leukemia, in terms of the dose equivalent of 1 Sv, was equal to 18.2 in those Japanese who were under 10 at the time of the atomic explosion and 2.44 for other cancers; whereas, for older age groups these figures were equal to 4.0–6.1 and 1.24–1.90, respectively (*3*).

For these reasons we included in the group under study those residents of the Leninsky Borough who at the time of the 1957 accident were under 15 years old. Of course, the same age limit (i.e., date of birth from 1942 to 1957) and the same criterion of living within the district since 1957 up to the present day (with possible breaks for studies or service in the army only) applied to the control group of residents from the Oktyabrsky Borough as well.

The controls were selected to match the cases by sex, age, and socio-occupational status. The basic method of mathematical data processing (see below) required that each individual be characterized by the same set of features; however, for some reasons this condition was not met with some of the subjects. Also, some of the subjects did not have a matched control; therefore, final analysis was based on data obtained from 52 matched pairs only who had complete data. (Data on the other subjects and controls were used for other purposes as described in the Discussion.) Matching groups and carefully choosing residential areas ensured maximum elimination of nonradioactive factors. Having completed the study, we found only three subjects in the experimental group and two controls had had to see doctors for some acute disease (or a relapse of a chronic disease) during the last 2 months before blood sampling.

Table 1. Indices used to characterize health status

Type	Tests
Hematological	Hemoglobin, red blood cell count, color index, leukocyte count, thrombocyte count, blood sedimentation rate, reticulocyte count and percent, segmented neutrophil count and percent, band neutrophil count and percent, total neutrophil count, neutrophil nuclear index, eosinophil count and percent, lymphocyte count and percent, monocyte count and percent, lymphocytogram (percent and number of large, medium, small, and large granulated lymphocytes)
Immunological	Percent and number of T-lymphocytes, percent and number of B-lymphocytes, teophilin-resistant (TRL) and teophilin-sensitive (TSL) lymphocytes, TRL/TSL ratio, IgA, IgE, IgG, IgM, complement, circulating immune complexes, nitrotetrasolium-blue test (NTB)
Biochemical	Malonyl dialdehyde, ceruloplasmin, antioxidant activity, superoxide dismutase, catalase, total cholesterol plus triglyceride content, albumin

Health status was characterized by a set of indices based on blood examination. Specifically, we estimated the cellular composition of blood, the performance of the immune system, and some biochemical processes including free-radical reactions. There is hardly any need to substantiate the choice of these indices as being informative for the purposes of revealing possible chronic radioactive damage. Again, the mathematical method required each index to be obtained for all the subjects compared; therefore, we did not use for analysis the indices that failed to meet this condition. The set of indices used is listed in Table 1.

The conditions of blood sampling, delivery of samples to the laboratories engaged in the experiment, as well as the techniques and conditions used in these studies were identical for the exposed and control groups. The differential blood count of each blood smear was carried out blindly by two qualified experts independently of each other. Each expert counted 200 white cells. The averages of the two experts' results were used in the analysis.

In addition to the average values and standard deviations of all the indices, multifactorial description of health status in the groups under comparison was carried out on the basis of the above indices, using the mathematical theory of pattern recognition and corresponding software employing various recognition algorithms (*4,5*). Specifically, we used the methodology known as "learning with a teacher," which had already been successfully applied to some other problems (*6–8*). According to this methodology, 15% of all the available observations are sampled into an "exam" group. The other observations are used by the computer as a basis for developing a discriminating rule, i.e., a rule that permits one to recognize a complex "image" of the members of groups under comparison based on the entire set of selected features, or on some subsets of features. Then this discriminating rule is tested on the "exam" group, and is accepted as satisfactory if it ensures no less than 80% correct recognitions (in our case, correct recognition of individuals as belonging to one of two groups). (In the case of a small number of observations, the reliability of exam results may be improved by sampling several variants of the exam group and checking the discriminating rule with each of them; this was done in the present study.)

The possibility of elaborating such a rule shows that these groups belong to different general sets, or, in our case, that the groups under comparison differ in generalized health status. The pattern recognition theory per se cannot tell us what caused this difference. Nevertheless, the described conditions of group formation and investigation suggest that the difference under consideration might be attributed to the inequality of radiation exposures.

The software used [the KVAZAR package developed at the Institute of Mathematics and Mechanics of the Ural Division of the Russian Academy of Sciences (*9*)] also permits one to quantitatively estimate the comparative informativeness of the features used in pattern recognition. The measure of informativeness is the Eukledean distance between the centers of the groups. Sequential elimination of the least informative of the features with repeat checks for exam recognition makes it possible to find a minimal subset of features which ensures reliable (i.e., no less than 80% correct) recognition. The KVAZAR software package also enables each feature to be estimated for the ability to increase the probability of referring an observation to a particular class (in our case the probability of referring an individual to the Leninsky or Oktyabrsky Borough).

Results and Discussion

The majority of the algorithms used for pattern recognition ensured 100% (or a little less) correct recognitions at the exam with the entire set of 51 features, but also with the hematological or immunological indices subsets only. The subset of biochemical indices alone did not ensure reliable recognition. To compare the informativeness of the features used, superoxide dismutase (SOD) activity was taken to be the most informative (value of 1), while the least informative feature (percent TFL-lymphocytes) was close to 0; the values of the rest of them varied from 0.708 (for the NTB-test) to 0.014 (for percent monocytes). We achieved quite reliable recognition using only five (but no less than five) most informative features, namely, SOD, nitrotetrasolium-blue test, circulating immune complexes, blood sedimentation rate, and the concentration of IgG (the informativeness of the latter was 0.436).

However, the best result (100% correct recognitions for both groups with a great number of discriminating rules based on different algorithms) was obtained using a subset comprising two most informative features from each of the three sets: immunological, hematological, and biochemical (irrespective of the rank of these six features in the general set of features). These features are listed in Table 2 along with their comparative informativenesss and group average values.

These six features might be suggested for a screening study in this city to select those residents (at least those born between 1942 and 1957) who need to be examined more carefully for damage to their health caused by the 1957 accident. This suggestion is in agreement with the results of the following experiment.

As mentioned in the previous section, some of the data could not be used in the elaboration of discriminating rules by the "learning" computer or for checking these results against the "exam" sample either because data on some of the required features were lacking or because subjects had no corresponding matched controls (or vice versa, controls had not corresponding subjects in the Leninsky Borough). Moreover, some of the blood samples were taken, for various reasons, from people who had been born before 1942. All these subjects were entered into the computer for recognition with the help of the set of six features. Ensuring fairly good recognition of the individuals born between 1942 and 1957 (which means that the consequences of the radioactive exposure are detectable), this subset, however, gave inferior results for individuals who were born before 1942. This provides indirect evidence that our choice of the most susceptible group was correct.

The comparative informativeness of the features used in this study is likely to be different in other circumstances of exposure to radiation and/or to other nonradioactive harmful factors. Nevertheless, the results show the adequacy of our methodological approach and recommend it for application to other problems of radioactive and ecological exposure.

Reliable recognition may be ensured using at least five informative features. However, if we consider each of these features separately, any single observation for any of its values may turn out to belong to either of the groups. At the same time, the probability of being recognized as belonging to these groups depends on the value of the index, this dependence being of two- or three-phase character. Thus, for instance, for minimal values an individual may be recognized as being a resident of the Leninsky Borough, and for high values as a member of the control group, these probabilities being practically equal in the range of medium values (i.e., in this range this feature lacks the discriminating power). In some cases the probabilities under consideration tended to be equal for maximal values as well.

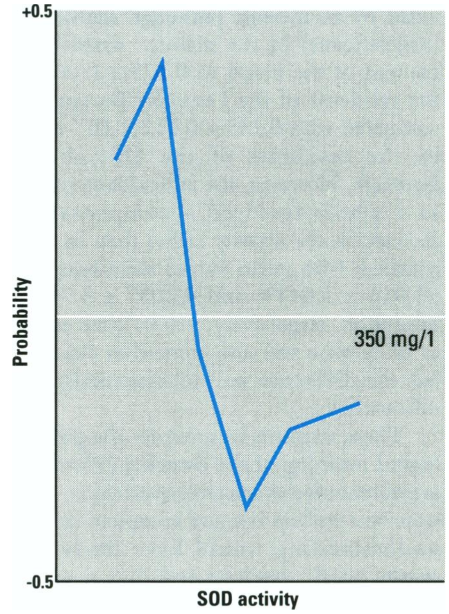

Figure 2. Probability of having been exposed to radiation versus detected level of activity of superoxide dismutase (SOD) in blood. Positive values on the ordinate indicate a higher probability of being a Leninsky Borough dweller; negative values indicate a higher probability of being an Oktyabrsky Borough dweller.

Figure 2 illustrates two-phase dependence of the probability of belonging to a group on the value of the most informative feature, i.e., SOD activity. The lower the activity, the more probable it is that a given individual is a resident of the Leninsky Borough. This corresponds to a substantial difference in the group-average values of SOD activity, which can presumably be explained by depletion of SOD in the antiradical protection mechanism, resulting from continuous enhancement of free-radical oxidation processes under the action of ionizing radiation. Indirect evidence of such enhancement (specifically, enhancement of lipoperoxidation) is pro-

Table 2. Comparative informativeness and mean values (±SE) of the features pertaining to the set that ensured reliable recognition of health status[a]

Feature	Informativeness	Mean values for groups: Leninsky	Mean values for groups: Oktyabrsky
Superoxide dismutase activity, µg/ml	1.000	96.54 ± 6.56	213.06 ± 11.30
Nitrotetrasolium-blue test (% of cells that ingested dye)	0.708	6.56 ± 1.31	20.86 ± 1.50
Circulating immune complexes (conventional units)	0.556	72.13 ± 3.59	47.26 ± 2.91
Blood sedimentation rate, mm/hr	0.462	11.44 ± 0.86	6.61 ± 0.88
Cholesterol + triglycerides, mg%	0.425	412.50 ± 23.44	291.61 ± 8.02
RBC count × 10^{12}/l	0.421	3.81 ± 0.05	4.08 ± 0.04

[a]Difference between the group-average values for each index is highly significant statistically (p<0.001, Student's t-test).

vided by an increase (although statistically insignificant) in the malonyl dialdehyde content of the blood to 0.173 ± 0.067 in the residents of the Leninsky Borough as compared with 0.139 ± 0.012 × 10^{-5} mol/l in the residents of the Oktyabrsky Borough. However, the antioxidant system as a whole featured a compensatory increase in the activity rather than its suppression (the mean values were equal to 53.016 ± 3.041% and 43.037 ± 3.797% inhibition, respectively, $p<0.01$); the activity of catalase was also somewhat elevated, but the difference was not statistically significant.

These attempts to interpret the physiological meaning of the detected differences are of tentative character; nevertheless, they were worthwhile because complete lack of understanding would have made our results purely tentative and thus not very reliable. From this viewpoint, for instance, a slight but statistically highly significant decrease in the RBC count (see Table 2), which is much easier to associate with exposure to radiation than an increase, may be interpreted as enhancing the reliability of our results on the whole. Judging from a sharp decrease in the nitrotetrasolium-blue test values, exposure to radiation suppressed the phagocytic protection mechanisms, while an increase in the concentration of IgG (16.945 ± 0.572 mg% and 12.624 ± 0.599 mg%, $p<0.001$) may reflect compensatory shifts in the humoral immunity system. The increased concentration of circulating immune complexes in the residents of the Leninsky Borough as compared with those of the Oktyabrsky Borough may indicate enhancement of some autoimmune processes. The same reason may account for the increase in the blood sedimentation rate (Table 2).

As for the increased level of cholesterol and triglycerides in the blood, we are inclined to think that, reflecting the intensity of atherosclerotic processes, the increased level is a sign of premature aging that may be regarded as a nonspecific delayed effect of long-term exposure to a multitude of harmful factors of relatively low efficiency. In particular, premature aging and early atherosclerotic changes were discovered in people several years after the Chernobyl accident who had been exposed to radiation doses that did not cause immediate unfavorable effects (*10*).

In conclusion, the pattern recognition methodology used in this study for detecting delayed effects of radioactive contamination permits one to reveal differences in the health status of residents that may be attributed to radiation exposure. We believe that this approach makes it possible to detect unfavorable effects of such exposure even against an unfavorable ecological background, and it can be used for handling other problems of this kind.

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